REMARKS

Claims 1-10, 16-20 and 22-45 are pending in the application. Claims 21 and 46-59 are withdrawn as drawn to non-elected inventions. Claims 11-15 have been canceled. Claims 1, 2, 4, 5, 17, 18, 22, 23, 24, 26, 27, 36, 37, and 40 have been amended to more clearly point out the claimed invention. Support for these amendments can be found throughout the specification and in the originally filed claims. No new matter has been added.

Rejections under 35 USC § 112, Second Paragraph

Claims 1-20 and 22-45 are rejected as being indefinite as the claims recite a method wherein the control sample is an individual or more than one individual. Claims 1, 2, 4, 5, 23, 26, 27, 37, and 40 have been amended to specify a method wherein the control sample is obtained from an individual or more than one individual. This rejection should be withdrawn.

Claims 1-20 and 22-45 are rejected as being indefinite for reciting a method wherein the control sample is determined using an EDSS or MRI. Claims 17 and 18 have been amended to specify a method wherein said group consisting of one or more individuals is determined using an EDSS assessment or an MRI assessment.

Claim 16 is rejected as being indefinite as it is unclear what is encompassed by "an early diagnosis" of MS. Applicants disagree. The term "early diagnosis" is a term used routinely in the art when referring to diagnosis of multiple sclerosis and one skilled in the art would understand what is meant by the claimed subject matter (see, e.g. US Patent No. 6,566,082, filed June 6, 1995, including abstract (Exhibit A), and Padmanabhan B., Role of MRI in diagnosing multiple sclerosis: early diagnosis using MRI and early treatment delays disease conversion. BMJ. 2006 Apr 29;332(7548):1034-5)(discussing studies examining the effect of MRI in early

diagnosis of MS) (Exhibit B); Whitney, Early Diagnosis and Intervention in Multiple Sclerosis, Int. J. MS Care, September 2001 (Exhibit C).

Claim 27 is rejected as being unclear what is intended by the claim. Claim 27 has been amended to specify a method wherein the control sample is obtained from a population of one or more individuals in exacerbated multiple sclerosis status, that show symptoms of a multiple sclerosis exacerbation.

Claims 1-20 and 21-45 are rejected for omitting essential steps. Claims 1, 2, 22, 24, and 36 have been amended to specify what is indicated by comparing levels of said antibody in the test sample to the levels of the antibody in a control sample.

Rejections under 35 USC § 112, First Paragraph

Claims 1-20 and 22-45 are rejected for lack of enablement. The rejection is traversed to the extent it is applied to the claims as amended.

The claims have been amended to specify isotypes of the recited antibodies that are shown in the specification to correlate with a disease status as disclosed in the specification. It is believed this amendment obviates the rejection to the extent it is based on the conclusion that levels of only certain antibody isotypes correlated with the presence of disease of its status.

The examiner also contends that the claims require undue experimentation in light of Schwarz et al., J. Neuro. Sci. 244:59-68, 2006 ("Schwarz"). This aspect of the rejection is addressed separately for claim 1, and for claims 22 and 36.

Claim 1, from which depend claims 2-20, as amended is drawn to a method of diagnosing multiple sclerosis in a subject by detecting the levels or an anti-Glc(α 1-4) Glc (α) antibody. The examiner states on page 4:

> [T]he Inventor's teach a number of embodiments wherein the claimed method would not diagnose or predict MS. For example, while certain antibodies might distinguish an MS patient from a health patient, the authors established that anti-Glc(α), anti-GlcNAc(α), and anti-Rha(α) antibodies would not distinguish MS patients from patients with other autoimmune diseases.

Applicants submit that the specification fully enables the claimed invention and provides examples illustrating the methods of claim 1. For example, the specification explains when summarizing data in FIG. 5 in Example 1:

> A comparison between the average and median values of anti-carbohydrate antibodies in the MS and normal populations reveals significant differences between the samples from the MS patients and the samples from the normal population, see FIG.5...The signal from bound antibodies in MS group is higher then the signal in the normal control group.

Similarly, the teachings of Schwarz in fact support the claimed invention. The reference states (pages 66-67):

> IgM anti-Gα4Gα antibody, which binds specifically to the sugar Glc(α1,4)Glc(α) antibody, is significantly higher in patients with MS (RR and PP) than in OND control group, and significantly higher in patients with RRMS than OAD.

Thus, both the specification and Schwarz suggest that amended claims 1-20 would not require undue experimentation. In view of the foregoing comments, Applicants request reconsideration and withdrawal of the rejection as applied to claims 1-20..

Claim 22, from which depends claims 23-35, is drawn to a method of diagnosing a multiple sclerosis disease exacerbation in a subject by detecting an anti- Glc (α 1-4) Glc (α) IgM type antibody. Claim 36, from which depend claims 37-45, is drawn to a method of assessing multiple sclerosis disease severity in a subject by determining whether the test sample contains an anti-Glc(α1-4) Glc(α) IgM type antibody. The specification explains when summarizing data in FIG. 7 in Example 3:

> The high specificity and sensitivity of the anti-Glc (α) and anti-Glc (α 1-4) Glc (α) IgM antibodies make them an efficient tool for early diagnosis and definition of MS patients. The fact that the levels of these antibodies in MS attack situation are much higher then in stable situation make them a tool for early identification and prediction of attacks in relapsing remitting MS patients.

Schwarz similarly states (page 65, first paragraph):

> Results presented in Table 3 reveal significantly higher levels of IgM anti-Gα4Gα in RRMS in comparison to OND ($p < 0.0001$), significant relative to OAD ($p = 0.02$), and no significant difference relative to PPMS. Significantly higher levels of IgM anti-Gα4Gα were detected in PPMS patients in comparison to OND patients. Anti-α-Glc and anti- α-Rha antibodies were significantly higher in patients with RRMS than in patients with OND ($p<<0.001$,), but were similar to the levels in patients with OAD and PPMS...No significant difference in the level of all four anti-glycan IgM antibodies was found between the treated and untreated RRMS patient groups, or between RRMS patient at relapse or remission.

A more detailed version of Table 3 in Schwarz, including segmentation to patients in relapse vs. patients in remission, reveals a statistical tendency differentiating between relapse patients and remission patients in these experiments (Exhibit G). The levels of anti-Glc (α1-4) Glc (α) and anti-Glc (α) IgM are higher in relapsing patients versus patients in remission. The levels of anti GlcNAc(α) IgM are almost significantly higher ($p=0.07$) than OAD, this as well, indicating the specificity of those antibodies to MS.

Although Schwarz reported that no significant difference in the level of all four anti-glycan IgM antibodies was found between treated and untreated RRMS patient groups, or between RRMS patients at relapse or remission, these findings do not compel a conclusion that these antibody levels cannot be used to predict relapse or to monitor the effectiveness of treatment. These types of assessment can only be performed in studies designed for this purpose, such as controlled prospective studies designed with continual follow-up patients, and using samples from untreated patients at the early stages of the diseases. The data in Schwarz, in contrast, represent a cross-sectional study of patients.

Additional post-filing evidence supports the enablement of the claimed methods. The ability of a panel of the above-mentioned anti-glycan antibodies to diagnose and predict the conversion of clinically isolated syndrome (CIS) to CDMS/RRMS was validated in recent Freedman, *et al.* published at the 21st and 22nd Congresses of the European Committee for the Treatment and Research in Multiple Sclerosis - ECTRIMS 2005 (Exbibit D) and 2006 (Exhibit E); and in Freedman, *et al.*, abstract accompanying an oral presentation at the 11th American Committee for the Treatment and Research in Multiple Sclerosis -ACTRIMS 2006 (Exhibit F); and Freedman et al., Anti-Glc(alph1,4)Glc(alpha) IgM antitibodies for predict the development of relapsing remitting multiple sclerosis after the first neurological event, 21st Congresss of the European Committee for the Treatment and Exhibit F. These studies report that hen used in conjunction with anti-Glc (α1-4) Glc (α) IgM antibody, anti α-Glc, anti α-GlcNAc, and anti α-Rha IgM antibodies differentially diagnose MS among other neurological diseases. These antibodies can also differentiate among MS subtypes.

In view of the foregoing comments, Applicants request reconsideration and withdrawal of the rejection.

Rejections under 35 USC § 102(b)

Claim 2 is rejected as anticipated by Mazzucco *et al.*, 1999 ("Mazzucco"). The rejection is traversed to the extent it is applied to the claim as amended.

Claim 2 depends from claim 1, which as amended is drawn to a method for diagnosing multiple sclerosis by detecting an anti-Glc(α1-4) Glc(α) IgM type antibody in a test sample. Claim 2 further requires that the method further includes detecting a second antibody that can be an anti-GlcNAc(α) IgM type antibody. Thus, claim 2 requires detecting both an anti-Glc(α1-4)

Glc(α) IgM type antibody and a second antibody that can be an anti-GlcNAc(α) antibody. Mazzucco does not describe a method of diagnosing multiple sclerosis that includes detecting both antibodies. For this reason alone, Mazzucco does not anticipate claim 2.

In addition, the GlcNAc(α) glycan recognized by the specified antibody in claim 2 differs from the glycol-peptide recognized by the antibody described by Mazzucco. The structural differences are marked in FIGS. 1A and 1B, below.

The GlcNAc glycan required by the claims is a glycan linked via an α linkage between the carbon atom in position 1 of the glucose and the terminal amine of asparagine (Asn). In contrast, the glycopeptide antigen described by Mazzucco includes a linkage in a β configuration between the carbon atom in position 1 (of the glucose) and the terminal amine of asparagine (Asn) amino acid. (See Mazzucco at page 169.) FIGS 1A and 1B show that the GlcNAc(a) glycan required by the claims includes an acetyl group linked via an amine bond to the carbon 2 atom on glucose. In contrast, Mazzucco describes a glycopeptide in which a D-Glucose binds to the terminal amine of the amino acid.

It is well-known in the art that structural differences significantly affect conformation and molecular behavior of the alternative isomers of a carbohydrate-containing molecule (See, e.g., Lehninger, Biochemistry 2nd Ed., 1975, pages 263-70.) For example, when D-Glucose structures bind each other in β 1-4 conformation (i.e., the 1 position in each glucose is bound to the 4th position in the other glucose), the resulting polymer is cellulose. When the same D-Glucose structures bind in an α 1-4 conformation, the resulting polymer remains an open chain known as Maltose and Amylose (soluble molecules found in the brain). Similarly, a polymer based on beta N-Acetyl Glucose amine (i.e. N-acetyl-beta-D-glucosamine β (1, 4)) is known as Chitin and is a hard insoluble polymer on the outer skeleton of insects and crabs. In contrast, a polymer based

on the alpha form (N-acetyl-beta-D-glucosamine-α (1, 4)) is known as a polysaccharide found in many bacterial species.

The remaining claims subject to the rejection depend from claims 1, 22 and 36. Thus, Mazzucco also fails to anticipate these claims. In view of the foregoing comments, Applicants request reconsideration and withdrawal of the rejection for anticipation.

Figure 1 A: The glycan moiety of the glycopeptides described by Mazzucco .Glucose residue in a beta configuration attached via the carbon atom in position 1 (of the glucose), to the terminal amine of asparagine (Asn) amino acid

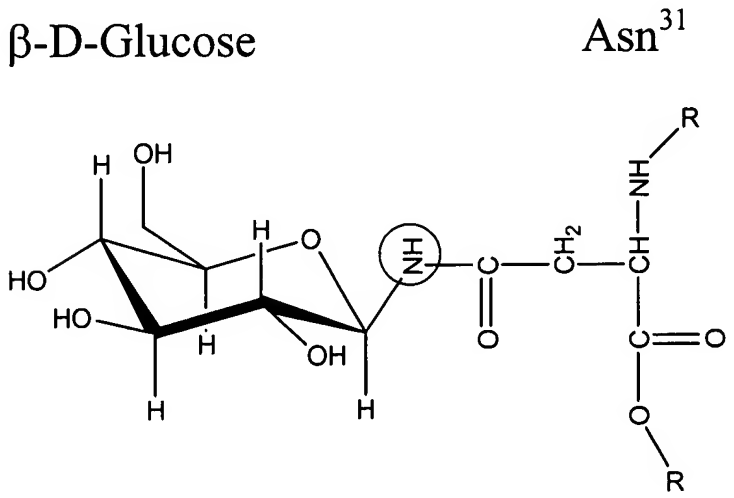
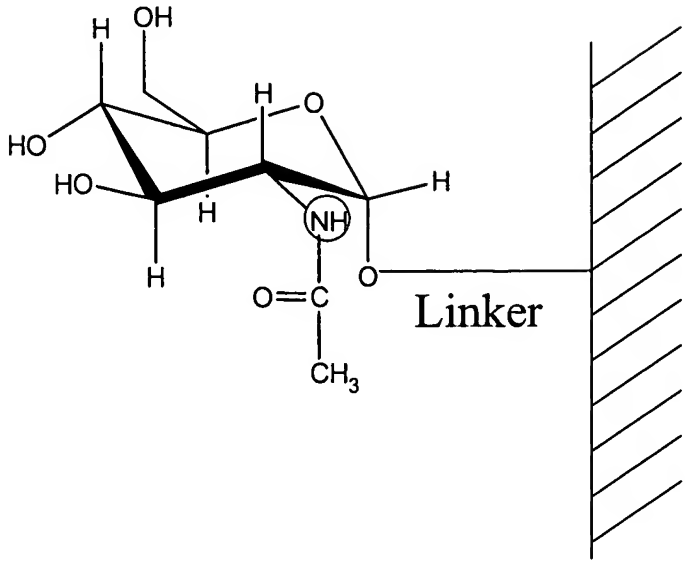


Figure 1 B : N-Acetyl alpha glucoseamine attached to solid phase via a linker.



Double patenting rejections

Claims 1-20 and 22-45 are provisionally rejected for obviousness-type double patenting over claims 1-20 and 22-45 of U.S. Application No. 10/835,607. Applicants will address this rejection upon the indication of allowable subject matter in either application.

Claims 1-20 and 22-45 are provisionally rejected for obviousness-type double patenting over claims 1-20 and 22-45 of U.S. Application No. 11/047,124. Applicants will address this provisional obviousness-type double patenting rejection upon the indication of allowable subject matter in either application.

Applicants submit that the application is in condition for allowance, and request a Notice for same. Please charge any fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311, Ref. No. 25681-501.

Respectfully submitted,

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